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Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 4: Tests for leachables in condensate

Évaluation de la biocompatibilité des voies de gaz respiratoires dans les applications de soins de santé —

Partie 4: Essais concernant les substances relargables dans le condensat

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the voluntary nature of ISO standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see the following URL: www.iso.org/iso/foreword.html.

The committee responsible for this document is ISO/TC 121, *Anaesthetic and respiratory equipment*, Subcommittee SC 3, *Lung ventilators and related equipment*.

A list of all parts of the ISO 18562 series can be found on the ISO website.

Introduction

This document is intended to protect PATIENTS connected to MEDICAL DEVICES from excessive amounts of harmful substances that might be contained in water that has condensed in the GAS PATHWAYS of those MEDICAL DEVICES. This document represents the application of the best-known science by addressing the RISKS from potentially hazardous substances in the condensate being conveyed to the PATIENT by the GAS PATHWAY. The condensate itself will be distilled water, having condensed from the vapour phase, but liquid water present in the breathing system might be able to leach or absorb other substances from within the MEDICAL DEVICE. This contamination might be from the original manufacturing PROCESS or be generated by the MEDICAL DEVICE itself during use.

This document is intended to cover the biological evaluation of GAS PATHWAYS of MEDICAL DEVICES within a RISK MANAGEMENT PROCESS, as part of the overall MEDICAL DEVICE evaluation and development. This approach combines the review and evaluation of existing data from all sources with, where necessary, the selection and application of additional tests.

In general, the ISO 10993 series is intended to cover the biological evaluation of MEDICAL DEVICES. However, the ISO 10993 series does not appropriately address the biological evaluation of the GAS PATHWAYS of MEDICAL DEVICES.

It is not within the scope of this document to address contamination arising from the source of the breathing gases entering such MEDICAL DEVICES, but rather only address the potential contamination generated from within the MEDICAL DEVICE itself. This contamination might be from the original manufacturing PROCESS or generated by the MEDICAL DEVICE itself during use.

This document is concerned with substances that could be conveyed to the PATIENT by liquid condensate forming in the MEDICAL DEVICE and then subsequently reaching the lungs of the PATIENT. Potentially harmful substances that could be found in condensate include salts and metals. Condensate management is part of most healthcare institution protocols, with the primary aim of preventing the condensate reaching the PATIENT in the first place. The absolute volume of liquid reaching a PATIENT by this route should therefore be low, but it might happen. This document outlines tests for substances contained in the liquid.

The methods to determine the acceptable levels of contamination are contained in ISO 18562-1.

In this document, the following print types are used:

— requirements and definitions: roman type;

— informative material appearing outside of tables, such as notes, examples and references: in smaller type. Normative text of tables is also in a smaller type;

— *test specifications: italic type*;

— terms defined in Clause 3 of this DOCUMENT or as noted: small capitals type.

In this document, the conjunctive "or" is used as an "inclusive or" so a statement is true if any combination of the conditions is true.

The verbal forms used in this document conform to usage described in Annex H of the ISO/IEC Directives, Part 2. For the purposes of this document, the auxiliary verb:

a) "shall" means that compliance with a requirement or a test is mandatory for compliance with this document;

b) "should" means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this document;

c) "may" is used to describe a permissible way to achieve compliance with a requirement or test.

An asterisk (*) as the first character of a title or at the beginning of a paragraph or table title indicates that there is guidance or rationale related to that item in Annex A.

The attention of Member Bodies is drawn to the fact that equipment manufacturers and testing organizations may need a transitional period following publication of a new, amended or revised ISO publication in which to make products in accordance with the new requirements and to equip themselves for conducting new or revised tests. It is the recommendation of the committee that the content of this publication be adopted for implementation nationally not earlier than 3 years from the date of publication for equipment newly designed and not earlier than 5 years from the date of publication for equipment already in production.

Biocompatibility evaluation of breathing gas pathways in healthcare applications —

Part 4: Tests for leachables in condensate

1 Scope

This document specifies tests for substances leached by liquid water condensing into GAS PATHWAYS of a MEDICAL DEVICE, its parts or ACCESSORIES, which are intended to provide respiratory care or supply substances via the respiratory tract to a PATIENT in all environments. The tests of this document are intended to quantify hazardous water-soluble substances that are leached from the MEDICAL DEVICE, its parts or ACCESSORIES by condensate and then conveyed by that liquid to the PATIENT. This document establishes acceptance criteria for these tests.

This document addresses potential contamination of the gas stream arising from the GAS PATHWAYS, which is then conducted to the PATIENT.

This document applies over the EXPECTED SERVICE LIFE of the MEDICAL DEVICE in NORMAL USE and takes into account the effects of any intended processing or reprocessing

This document does not address biological evaluation of the surfaces of GAS PATHWAYS that are in direct contact with the PATIENT. The requirements for direct contact surfaces are found in the ISO 10993 series.

MEDICAL DEVICES, parts or ACCESSORIES containing GAS PATHWAYS that are addressed by this document include, but are not limited to, ventilators, anaesthesia workstations (including gas mixers), breathing systems, oxygen conserving devices, oxygen concentrators, nebulizers, low-pressure hose assemblies, humidifiers, heat and moisture exchangers, respiratory gas monitors, respiration monitors, masks, mouth pieces, resuscitators, breathing tubes, breathing systems filters, Y-pieces and any breathing ACCESSORIES intended to be used with such devices. The enclosed chamber of an incubator, including the mattress, and the inner surface of an oxygen hood are considered to be GAS PATHWAYS and are also addressed by this document.

This document does not address contamination already present in the gas supplied from the gas sources while MEDICAL DEVICES are in NORMAL USE.

EXAMPLE Contamination arriving at the MEDICAL DEVICE from gas sources such as MEDICAL GAS PIPELINE SYSTEMS (including the non-return valves in the pipeline outlets), outlets of pressure regulators connected or integral to a medical gas cylinder, or room air taken into the MEDICAL DEVICE is not addressed by ISO 18562 series.

This document does not address contact with drugs or anaesthetic agents. If a MEDICAL DEVICE is intended to be used with anaesthetic agents or drugs, then additional testing can be required.

This document is intended to be read in conjunction with ISO 18562-1.

NOTE This document has been prepared to address the relevant essential principles of safety and performance as indicated in Annex B.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 7396-1:2016, *Medical gas pipeline systems — Part 1: Pipeline systems for compressed medical gases and vacuum*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-5, *Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity*

ISO 10993-10, *Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization*

ISO 10993-12:2012, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 14971:2007, *Medical devices — Application of risk management to medical devices*

ISO 18562-1:2017, *Biocompatibility evaluation of breathing gas pathways in healthcare applications — Part 1: Evaluation and testing within a risk management process*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 7396-1, ISO 14971 and ISO 18562-1 apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at http://www.iso.org/obp

NOTE For convenience, an alphabetized index of all defined terms and their sources used in this document are given in Annex C.

4 General principles

4.1 TYPE TESTS

The tests described in this document are TYPE TESTS. TYPE TESTS are performed on the final MEDICAL DEVICE, a component of the MEDICAL DEVICE or a representative sample of the MEDICAL DEVICE, part or ACCESSORY being evaluated. If representative samples are used, (i.e. manufactured and processed by equivalent methods), consideration should be made regarding whether or not the differences between the representative sample and the final MEDICAL DEVICE or component could affect the results of the test. Testing of representative samples (manufactured and processed by equivalent methods) instead of the final MEDICAL DEVICE should be supported by a description of any differences between the representative sample and the final MEDICAL DEVICE, and a detailed rationale for why each difference is not expected to impact the BIOCOMPATIBILITY of the final MEDICAL DEVICE.

NOTE Some AUTHORITIES HAVING JURISDICTION evaluate these differences and rationales.

4.2 General

All GAS PATHWAYS from which the PATIENT inspires gas shall be evaluated using the strategy detailed in ISO 18562-1.

5 LEACHABLE SUBSTANCES in condensate

5.1 General

A MEDICAL DEVICE, part or ACCESSORY shall not add to the condensate LEACHABLE SUBSTANCES at levels that create an unacceptable RISK to the PATIENT. All GAS PATHWAYS from which the PATIENT inspires gas in NORMAL CONDITION, where

— gas in the GAS PATHWAY can reach 100 % saturation with water at some point in the GAS PATHWAY,

— condensate can form on the GAS PATHWAY surfaces, and

— liquid condensate can reach the PATIENT,

shall be evaluated for condensate emissions. The evaluation should use the RISK MANAGEMENT PROCESS to assess if testing is required.

NOTE 1 Condensate can form in GAS PATHWAYS and can take the form of liquid drops or a film of water on the GAS PATHWAY walls. This liquid water can extract substances from the materials of the walls that would not be extracted by the breathing gas alone. If this liquid condensate can reach the PATIENT, it could potentially convey harmful substances to the PATIENT.

NOTE 2 The evaluation of some components, which are identical in FORMULATION, processing and preparation for use to an existing component of a MEDICAL DEVICE that has been previously tested, might conclude that no further testing is required. Refer to ISO 18562-1:2017, Figure 2.

Sections of the GAS PATHWAY from which the PATIENT cannot be exposed to condensate need not be tested.

If the RISK MANAGEMENT PROCESS determines that testing is required, the tests of 5.2 shall be performed.

If the MEDICAL DEVICE under evaluation has already been evaluated as an external communicating MEDICAL DEVICE with contact to tissue/bone/dentin according to ISO 10993-1, then the following tests need not be performed.

EXAMPLE A tracheal tube, because of its direct contact with the PATIENT, is evaluated according to ISO 10993-1. In this case, the tests of this document are not required.

NOTE 3 Some AUTHORITIES HAVING JURISDICTION might require these tests if the MEDICAL DEVICE is intended for use on particularly vulnerable PATIENT populations, such as neonates.

5.2 * Test method

Test for LEACHABLE SUBSTANCES in condensate is as follows.

a) To collect a sample, either

   1) produce and collect condensate under clinically relevant conditions, or

   2) circulate the water over the surface of the sample at a temperature representative of clinical use, or

   3) * perform an aqueous extraction on the internal gas contact surfaces according to the method of ISO 10993-12:2012, Clause 10, with the extract at clinically relevant temperatures, for a clinically relevant duration of time.

   EXAMPLE There is no clinical relevance to performing a 24-h extraction on a MEDICAL DEVICE that is only intended to be used on a PATIENT for 20 min. However, the underlying principle remains "what is the dose to the PATIENT in 24 h". If a MEDICAL DEVICE could be used multiple times in a 24-h period, then the maximum likely cumulative time is considered. Additionally, if the MEDICAL DEVICE is consumable and replaced consecutively, the 24-h exposure can be higher due to additive effects.

   NOTE 1 See the rationale in Annex A for further considerations if performing an aqueous extraction.

This document is not intended to be prescriptive in the selection of MEDICAL DEVICE configuration, test method and conditions used to produce the sample. Choices should be justified and documented.

b) * Determine the content of metal ions in the condensate or extract using the method of pharmacopeias (e.g. USP<233>[17]) or another relevant method. Evaluate the results based on limits defined in USP<232>[18] or other validated sources. If not all the metals listed in USP<233> are screened for, then justify and document the rationale.

NOTE 2 Similar analytical methods are useful to assess other metals of concern, such as nickel and chromium.

If exposure limits are not available for specific metals identified in condensate, then derive a TOLERABLE INTAKE using the method of ISO 18562-1:2017, Clause 7.

Convert the concentration of each metal ion to a total dose/day by considering the total amount of liquid condensate that reaches the PATIENT in a day as 1 ml.

c) * If required in order to achieve detection of concentrations at the limits specified, enrich the organic impurities in the condensate or extract using established methods, such as stir bar sorptive extraction, solid phase microextraction, liquid-liquid extraction or a demonstrably equivalent method. Then identify and quantify organic impurities using GC-MS (gas chromatography-mass spectrometry) or an equivalent method.

Convert the concentration of each substance to a total dose per PATIENT per day by considering the total amount of condensate that reaches the PATIENT per day as 1 ml.

Confirm that the dose of each identified substance delivered to the PATIENT in 1 ml of condensate or extract is less than the TOLERABLE INTAKE or THRESHOLD OF TOXICOLOGICAL CONCERN derived from the method of ISO 18562-1:2017, Clause 7.

The route of exposure is into the lung and therefore considered inhalational, not oral ingestion.

d) * Perform a cytotoxicity test according to ISO 10993-5 on the condensate or extract. There are several different methods offered in ISO 10993-5. Select a method suitable for liquids.

NOTE 3 The MEM elution method is a sensitive method, and is normally accepted by AUTHORITIES HAVING JURISDICTION as an appropriate method.

e) * Perform a sensitization test according to ISO 10993-10 on the condensate or extract. Select a method suitable for liquids.

NOTE 4 The LLNA method is normally accepted by AUTHORITIES HAVING JURISDICTION as an appropriate method. However, there are concerns that this particular test method might not be wholly suitable if

— the MEDICAL DEVICE includes nickel,

— the extract contains a mixture of substances, rather than a single leached substance,

— the aqueous extract does not include a vehicle to ensure the extract is in contact with the skin, or

— novel materials that do not penetrate the skin are present (e.g. nanomaterials).

Annex A
(informative)

Rationale and guidance

A.1 General guidance

This annex provides rationale for the important requirements of this document and is intended for those who are familiar with the subject of this document, but who have not participated in its development. An understanding of the reasons for the main requirements is considered to be essential for its proper application. Furthermore, as clinical practice and technology change, it is believed that rationale for the present requirements will facilitate any revision of this document necessitated by those developments.

The clauses and subclauses in this annex have been so numbered to correspond to the clauses and subclauses in this document to which they refer. The numbering is, therefore, not consecutive.

A.2 Rationale for particular clauses and subclauses

5.2 — Test method

a) 3)

Typically, the extraction ratio will be 3 cm^2 of inner GAS PATHWAY surface per ml of water.

Care should be taken if the bulk material of the walls of the GAS PATHWAY are non-homogeneous. For example, a tube with a coating or a co-extruded tube could have different materials on the inner gas contact surfaces from the materials forming the outer surfaces. In this case, grinding up the bulk material to perform the extraction will not give results representative of an intact tube.

Also, be aware that with some materials, fresh cut surfaces can have different properties from the surfaces resulting from the actual manufacturing PROCESS. For example, extruded foamed materials typically have a closed film surface, while the inner bulk material has a foam structure with a much greater surface area. These two different physical forms of the same material may well give different results when a typical extraction is performed.

Some AUTHORITIES HAVING JURISDICTION recommend exhaustive extraction for prolonged and permanent duration MEDICAL DEVICES.

b)* and *c)

In any assessment, the most important consideration is the actual dose-to-PATIENT, which is calculated by taking the concentrations multiplied by the volume the PATIENT inhales or ingests per day.

The experts on the committee discussed at length the amount of liquid condensate that might reach the PATIENT per day. The committee noted that it is established clinical practice to have methods in place to prevent liquid water as condensate from reaching the PATIENT. These methods include heated breathing hoses and water traps. The committee concluded that having condensed water reaching the PATIENT was bad clinical practice and was an anomalous event, not a regular occurrence.

The committee decided that as ISO 14971 requires them to consider intended and reasonably foreseeable misuse, the daily permitted volume of water entering a PATIENT should be set at 1 ml. This value of 1 ml should be used in the calculations to derive the dose to the PATIENT. The condensate enters the lungs. The dose is therefore compared with derived limits for inhalation, not oral ingestion.

d) and ***e)***

Historically, a MEDICAL DEVICE with a breathing GAS PATHWAY, which exposed a PATIENT to LEACHABLE SUBSTANCES in condensate, was evaluated as externally communicating with contact to tissue/bone/dentin according to ISO 10993-1. As such, the MEDICAL DEVICE was evaluated for a range of biological effects, including local and systemic endpoints. The TOLERABLE INTAKE and THRESHOLD OF TOXICOLOGICAL CONCERN methodologies principally address systematic effects (e.g. carcinogenicity), but are also adequately protective for many local effects (e.g. irritation).

Cytotoxicity testing has been retained, as these tests are very sensitive and serve as a screening test for local effects.

Sensitization testing (in-vivo) has been retained as the TI and TTC methodologies are not adequately predictive, and no in-vitro methods are known to be adequate.

Annex B
(informative)

Reference to the essential principles

This document has been prepared to support the essential principles of safety and performance of GAS PATHWAYS as components of MEDICAL DEVICES according to ISO 16142-1[16]. This document is intended to be acceptable for conformity assessment purposes.

Compliance with this document provides one means of demonstrating conformance with the specific essential principles of ISO 16142-1[16]. Other means are possible. Table B.1 maps the clauses and subclauses of this document with the essential principles of ISO 16142-1.

Table B.1 — Correspondence between this document and the essential principles

Essential principle of ISO 16142-1:2016[16]	Corresponding clause(s)/ subclause(s) of this document	Qualifying remarks/notes
8.1 a)	Clause 4, Clause 5	Only the part relating to toxicity is addressed.
8.1 b)	Clause 4, Clause 5	
8.2	Clause 4, Clause 5	
8.4	Clause 4, Clause 5	
8.5	Clause 4, Clause 5	Only the part relating to egress of substances from the MEDICAL DEVICE is addressed.

Annex C
(informative)

Terminology — Alphabetized index of defined terms

NOTE The ISO Online Browsing Platform (OBP)[1)] and the IEC Electropedia[2)] provide access to many of these terms and definitions.

Term	Source
accessory	ISO 18562-1:2017, 3.1
authority having jurisdiction	ISO 16142-1:2016, 3.1
biocompatibility	ISO 18562-1:2017, 3.2
expected service life	ISO 18562-1:2017, 3.3
formulation	ISO 18562-1:2017, 3.4
gas pathway	ISO 18562-1:2017, 3.5
hazard	ISO 14971:2007, 2.3
leachable substances	ISO 18562-1:2017, 3.6
medical device	ISO 18562-1:2017, 3.7
medical gas pipeline system	ISO 7396-1:2016, 3.29
normal condition	ISO 18562-1:2017, 3.8
normal use	ISO 18562-1:2017, 3.9
patient	ISO 18562-1:2017, 3.11
process	ISO 14971:2007, 2.13
risk	ISO 14971:2007, 2.16
risk management	ISO 14971:2007, 2.22
tolerable intake	ISO 18562-1:2017, 3.14
type test	ISO 18562-1:2017, 3.15

1) Available at: https://www.iso.org/obp/ui/#home

2) Available at http://www.electropedia.org/

Bibliography

[1] ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

[2] ISO 10993-3, *Biological evaluation of medical devices — Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

[3] ISO 10993-4, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood*

[4] ISO 10993-6, *Biological evaluation of medical devices — Part 6: Tests for local effects after implantation*

[5] ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

[6] ISO 10993-9, *Biological evaluation of medical devices — Part 9: Framework for identification and quantification of potential degradation products*

[7] ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

[8] ISO 10993-13, *Biological evaluation of medical devices — Part 13: Identification and quantification of degradation products from polymeric medical devices*

[9] ISO 10993-14, *Biological evaluation of medical devices — Part 14: Identification and quantification of degradation products from ceramics*

[10] ISO 10993-15, *Biological evaluation of medical devices — Part 15: Identification and quantification of degradation products from metals and alloys*

[11] ISO 10993-16, *Biological evaluation of medical devices — Part 16: Toxicokinetic study design for degradation products and leachables*

[12] ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

[13] ISO 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of materials*

[14] ISO/TS 10993-19, *Biological evaluation of medical devices — Part 19: Physico-chemical, morphological and topographical characterization of materials*

[15] ISO/TS 10993-20, *Biological evaluation of medical devices — Part 20: Principles and methods for immunotoxicology testing of medical devices*

[16] ISO 16142-1:2016, *Medical devices — Recognized essential principles of safety and performance of medical devices — Part 1: General essential principles and additional specific essential principles for all non-IVD medical devices and guidance on the selection of standards*

[17] USP 35 — NF 30, Chapter 233-Elemental impurities-procedures, February 1, 2013. Available (viewed 2016-06-28) at: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/key-issues/233----2s_usp_35---final.pdf

[18] USP 35 — NF 30, Chapter 232-Elemental impurities-limits, February 1, 2013. Available (viewed 2016-06-28) at: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/key-issues/c232_final.pdf